An Age-specific Kinetic Model of Lead Metabolism in Humans

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Although considerable progress has been made in recent years in reducing human exposures to lead, the potential for high intake of this contaminant still exists in millions of homes and in many occupational settings. Moreover, there is growing evidence that levels of lead intake considered inconsequential just a few years ago can result in subtle, adverse health effects, particularly in children. Consequently, there have been increased efforts by health protection agencies to develop credible, versatile methods for relating levels of lead in environmental media to levels in blood and tissues of exposed humans of all ages. In a parallel effort motivated largely by the Chernobyl nuclear accident, the International Commission on Radiological Protection (ICRP) is assembling a set of age-specific biokinetic models for calculating radiation doses from environmentally important radionuclides, including radioisotopes of lead. This paper describes a new age-specific biokinetic model for lead originally developed for the ICRP but expanded to include additional features that are useful for consideration of lead as a chemical toxin. The model is developed within a generic, physiologically motivated framework designed to address a class of calciumlike elements. This framework provides a useful setting in which to synthesize experimental, occupational, and environmental data on lead and exploit common physiological properties of lead and the alkaline earth elements. The modular design is intended to allow researchers to modify specific parameter values or model components to address special problems in lead toxicology or to incorporate new information. Transport of lead between compartments is assumed to follow linear, first-order kinetics provided the concentration in red blood cells remains below a nonlinear threshold level, but a nonlinear relation between plasma lead and red blood cell lead is modeled for concentrations above that level. The model is shown to be consistent with data on human subjects exposed to lead under a variety of experimental and natural conditions. *Key words:* age-specific metabolism, biokinetics, kinetic model, lead. *Environ Health Perspect* 101:598–616(1993)

Despite an overall decrease in human exposure to lead in recent years (*1–4*), the potential for high intake of this contaminant still exists in millions of homes and in many occupational settings. Moreover, there is growing evidence that levels of lead intake considered inconsequential just a few years ago can result in a variety of subtle, adverse health effects in the absence of overt intoxication (*4–7*). Lead poses a particularly great threat to young children, who have elevated contact with lead in dust, soil, and paint, elevated gastrointestinal absorption of lead, elevated turnover of bone lead into blood, and incompletely developed organs and defense mechanisms.

The growing awareness of the health threat posed by lead has stimulated increased efforts to develop a detailed characterization of the biological behavior of lead in humans of all ages. Several biokinetic models for lead have now been published (*8–20*). Most of these were derived as curve fits to limited data from controlled metabolic studies on adult human volunteers or laboratory animals at different stages of life. In some cases an attempt has been made to improve upon such exposure-specific characterizations of lead metabolism by synthesizing data from a variety of exposure conditions (*18,19*) or introducing greater physiological realism into the modeling process (*15,20*).

In an effort motivated largely by the Chernobyl nuclear accident, the International Commission on Radiological Protection (ICRP) is assembling a set of age-specific biokinetic models for environmentally important radioelements (*21,22*). To this point, models for bone-seeking elements have been developed within one of two generic model structures. One of these applies to the "bone-surface-seeking" elements, including plutonium, americium, neptunium, and thorium (*23*). The other applies to the "bone-volume-seeking" or "calciumlike" elements, including strontium, barium, radium, and lead. Each of these model frameworks represents a workable compromise between biological realism and practical considerations regarding the amount and quality of information available to determine parameter values. The generic structure for the calciumlike elements provides a useful setting in which to synthesize experimental, occupational, and environmental data on lead and to exploit common physiological properties of lead and the alkaline earth elements.

The purposes of this paper are to explain the conceptual basis of the lead model as developed for the ICRP and expand that model to include features that are useful for consideration of lead as a chemical toxin but that are unimportant for consideration of lead as a radiological toxin. In contrast to the version of this model developed for the ICRP, the expanded version includes a relatively detailed description of circulating lead, a concentration-dependent transfer rate into red blood cells (provided the lead concentration in red blood cells exceeds a specified threshold level), and consideration of the brain as a separate compartment.

Brief Overview of the Model

The model describes the time-dependent distribution and excretion of lead that has been injected or absorbed into blood. This systemic model may be used in conjunction with any model describing the translocation of lead from the respiratory or gastrointestinal tract into blood. The respiratory and gastrointestinal models used in the present paper to evaluate human exposure data or to compare model predictions with observations of the fate of inhaled or ingested lead are described in the appendix.

A schematic diagram of the compartments used in the systemic model and directions of movement of lead among these compartments is given in Figure 1. A more detailed schematic diagram of the circulation, i.e., the model for lead in blood and rapidly exchanging extravascular fluids, is shown in Figure 2.

Transport of lead between compartments is assumed to follow first-order kinetics provided the concentration in red blood cells (RBCs) stays below a nonlinear threshold concentration. When the concentration in RBCs exceeds that threshold, the transfer rate from diffusible plasma to RBCs is assumed to decrease as the concentration in RBCs increases. At the same time, the deposition fractions in other compartments are increased due to decreased

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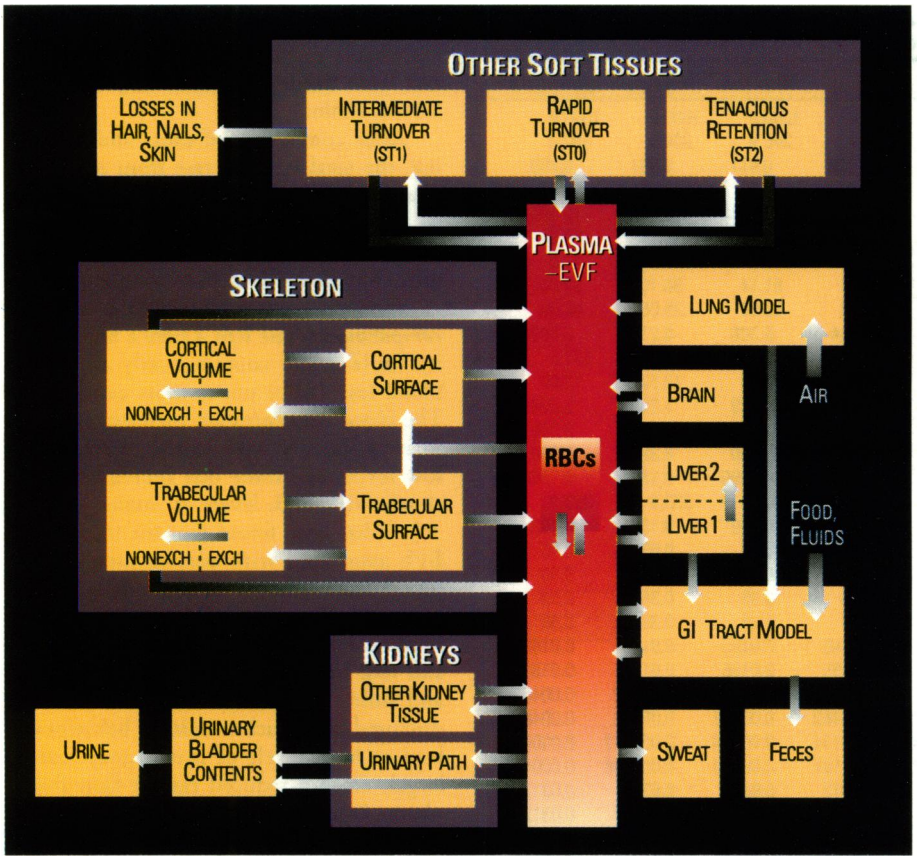


Figure 1. Compartments and paths of movement in the biokinetic model for lead. The systemic model may be used in conjunction with any model of absorption from the lungs or gastrointestinal tract. The "plasma-EVF" box, including RBCs, represents the model of the circulation, which is shown in more detail in Figure 2.

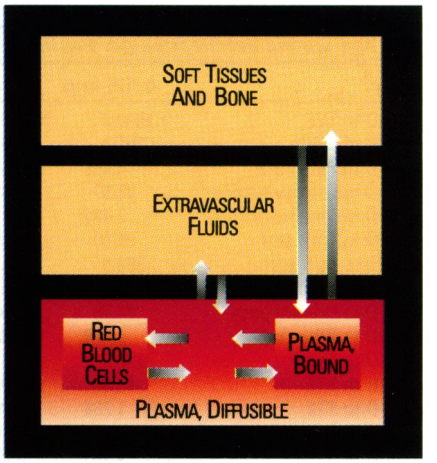


Figure 2. Model of the circulation. Diffusible plasma is viewed as the central feeding compartment and extravascular fluids (EVF) are treated as a satellite compartment. Lead that moves between plasma and retention sites in tissues is treated, in effect, as if it passed instantaneously through the EVF.

competition from the RBCs, but first-order transport between all other compartments is assumed to be maintained at all levels of exposure. A nonlinear threshold concentration of 60 µg/dl RBC (corresponding to a blood lead concentration of about 25 µg/dl) is assigned.

Transfer rates between compartments are given in Table 1 for the six age groups considered in Publication 56 of the International Commission on Radiological Protection (*21,22*). Transfer rates for ages intermediate to those addressed in Table 1 are obtained by interpolating linearly with age between the listed rates. For example, a transfer rate for age 4 years is calculated as 0.25 times the rate given for age 1 year plus 0.75 times the rate given for age 5 years. Changes with age in the biokinetics of lead during adulthood are not addressed here, but variation with adult age in the rate of bone turnover, in particular, can easily be included in the model if desired (*23,24*).

Several software packages are available for solving the type of compartmental model described here. A particularly elementary and efficient method of solution developed at this laboratory is described in a recent paper (*25*).

Definitions

The "removal half-time" from a compartment refers here to the biological half-time that one would observe, theoretically, if outflow from that compartment continued while feeds from all other compartments were stopped. The removal half-time is shorter than the apparent half-time in the presence of recycling. For example, with the model structure used here, the estimated removal half-time from RBCs to diffusible plasma is 5 days, but the half-time in RBCs that is apparent to the outside observer is a few weeks because the RBCs continually take up lead that has been released to plasma from bone, soft tissues, and RBCs.

The term "transfer rate" as used here indicates fractional transfer per unit time from one compartment to another. (Note that the transfer rates in this model are not actually rate "constants" because in many cases they change with age and hence time.) The "total transfer rate" from a compartment refers to the sum of transfer rates from that compartment to all destinations. For example, the total transfer rate from diffusible plasma to all other compartments is estimated as 2000/day, which corresponds to a removal half-time from diffusible plasma of $\ln(2)/(2000/\text{day}) = 0.00035$ day = 0.5 min. Parameter values are expressed as transfer rates (per day) between compartments because software packages for implementing compartmental models usually require transfer rates as input. Most of the derived transfer rates are secondary values, however, calculated from selected removal half-times and deposition fractions.

The term "deposition fraction" as used here refers to instantaneous fractional outflow from the diffusible plasma compartment. For example, a deposition fraction of 0.24 is assigned to RBCs. This means that 24% of the lead atoms leaving plasma in a short time (seconds) are assigned to the RBCs compartment. Since the total transfer rate from diffusible plasma to all destinations combined is estimated as 2000/day, the transfer rate from diffusible plasma to RBCs is $0.24 \times (2000/\text{day}) = 480/\text{day}$. The use of deposition fractions provides one way of introducing consideration of material balance and competition between compartments into the selection of parameter values. This also provides a convenient way to relate model parameters to data on the early distribution of tracer lead. In the present model, a deposition fraction, F, for a compartment other than the rapid turnover compartment, EVF (which is assumed to equilibrate with diffusible plasma within a few minutes after injection of lead into blood) indicates that the compartment accumulates roughly $2 \times F \times 100\%$ of the initial input to blood during the first hour or so after injection. This is because compartment EVF is assigned a deposition fraction of 0.5 and thus receives about half of the injected amount within minutes. This initial inflow into EVF rapidly redistributes to the other compartments, virtually doubling the contents of those compartments over a short time.

Table 1. Age-specific transfer rates (per day) for the model indicated in Figures 1 and 2[a]

Pathway[b]	0–100 days	1 year	5 years	10 years	15 years	≥ 25 years
Plasma-D to EVF	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0
Plasma-D to RBCs	297.1	406.9	425.1	366.9	300.6	480.0
Plasma-D to Plasma-B	0.495	0.678	0.709	0.611	0.501	0.800
Plasma-D to Urinary bladder[c]	18.57	25.43	26.57	22.93	18.79	30.00
Plasma-D to Small intestine[d]	7.429	10.171	10.629	9.171	7.514	12.000
Plasma-D to Trab surf	96.00	57.60	56.83	89.50	132.25	88.96
Plasma-D to Cort surf	384.0	230.4	199.2	268.5	341.8	71.0
Plasma-D to Liver 1	49.52	67.81	70.86	61.14	50.10	80.00
Plasma-D to Urinary path	24.76	33.90	35.43	30.57	25.05	40.00
Plasma-D to Other kidney	0.248	0.339	0.354	0.306	0.250	0.400
Plasma-D to ST0	103.3	141.5	148.4	128.0	104.9	177.5
Plasma-D to ST1	12.38	16.95	17.71	15.29	12.52	10.00
Plasma-D to ST2	1.238	1.695	1.771	1.529	1.252	2.000
Plasma-D to Brain	0.557	0.763	0.266	0.229	0.188	0.300
Plasma-D to Sweat	4.333	5.933	6.200	5.350	4.383	7.000
RBCs to Plasma-D	0.4620	0.4620	0.2770	0.1390	0.1390	0.1390
EVF to Plasma-D	333.3	333.3	333.3	333.3	333.3	333.3
Plasma-B to Plasma-D	0.139	0.139	0.139	0.139	0.139	0.139
Cort surf to Plasma-D	0.65	0.65	0.65	0.65	0.65	0.50
Trab surf to Plasma-D	0.65	0.65	0.65	0.65	0.65	0.50
Cort surf to Exch vol	0.35	0.35	0.35	0.35	0.35	0.50
Trab surf to Exch vol	0.35	0.35	0.35	0.35	0.35	0.50
Cort exch vol to Surf	0.0185	0.0185	0.0185	0.0185	0.0185	0.0185
Trab exch vol to Surf	0.0185	0.0185	0.0185	0.0185	0.0185	0.0185
Cort exch vol to Nonexch vol	0.00462	0.00462	0.00462	0.00462	0.00462	0.00462
Trab exch vol to Nonexch vol	0.00462	0.00462	0.00462	0.00462	0.00462	0.00462
Cort nonexch vol to Plasma-D	0.00822	0.00288	0.00154	0.00089	0.000512	0.0000822
Trab nonexch vol to Plasma-D	0.00822	0.00288	0.00181	0.00132	0.000956	0.000493
Liver 1 to Plasma-D	0.0312	0.0312	0.0312	0.0312	0.0312	0.0312
Liver 1 to Small intestine	0.0312	0.0312	0.0312	0.0312	0.0312	0.0312
Liver 1 to Liver 2	0.00693	0.00693	0.00693	0.00693	0.00693	0.00693
Liver 2 to Plasma-D	0.00693	0.00693	0.00693	0.00190	0.00190	0.00190
Urinary path to Urinary bladder	0.139	0.139	0.139	0.139	0.139	0.139
Other kidney to Plasma-D	0.00693	0.00693	0.00693	0.00190	0.00190	0.00190
ST0 to Plasma-D	2.079	2.079	2.079	2.079	2.079	2.079
ST1 to Plasma-D	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416
ST1 to Excreta	0.00277	0.00277	0.00277	0.00277	0.00277	0.00277
ST2 to Plasma-D	0.00038	0.00038	0.00038	0.00038	0.00038	0.00038
Brain to Plasma-D	0.00095	0.00095	0.00095	0.00095	0.00095	0.00095

[a]Transfer rates for ages intermediate to those addressed in Table 1 are obtained by interpolating linearly with age between the listed rates. For example, a transfer rate for age 4 years is calculated as 0.25 times the rate given for age 1 year plus 0.75 times the rate given for age 5 years.
[b]Plasma-D and plasma-B are diffusible and bound plasma compartments; trab and cort indicate trabecular and cortical bone; surf and vol indicate bone surface and volume, and exch and nonexch indicate exchangeable and nonexchangeable bone.
[c]For most purposes, it suffices to assume instantaneous transfer from urinary bladder to urine.
[d]There is also assumed transfer from the small intestine back to diffusible plasma. The assigned rate depends on the choice of a gastrointestinal tract model (see appendix).

Model for Adults

Circulation

Basis for two plasma compartments. Soon after introduction of a lead tracer (radiolead) into blood plasma, the tracer is largely available for diffusion into extravascular fluids and filtration by the kidneys (*26–28*). Under steady-state conditions, however, most of the plasma lead apparently is bound to proteins, with α–globulin having a particularly high lead-binding capacity (*29,30*). Two plasma compartments are needed to depict a gradual shift of a large portion of plasma lead to nondiffusible plasma proteins (Fig. 2). Lead injected or absorbed into blood or returning to blood from the extravascular spaces is assigned to the diffusible compartment within plasma, from which it transfers rapidly to the extravascular spaces and RBCs. A tiny fraction of the total outflow from diffusible plasma is assigned to a protein-bound compartment of plasma that returns lead slowly to diffusible plasma and eventually contains most of the plasma lead.

Total transfer rate from diffusible plasma (to all destinations). Immediately after intravenous injection of radiolead into adult humans, activity disappears from blood at a rate of about 1/min (*27,31–33*), which is similar to the rate determined for radiocalcium in human subjects (*34*). The assigned transfer rate of lead from diffusible plasma to all destinations should be somewhat higher than 1/min, however, to account for rapid uptake by RBCs (Fig. 3) as well as transfer to the extravascular spaces (*27,28,31*). A reasonable estimate of the total transfer rate from diffusible plasma may be about 1.3– 1.4/min.

After conversion of units and rounding, the total removal rate from diffusible plasma to all destinations is set at 2000/day. As explained in a previous section, this value is used to calculate transfer rates from diffusible plasma to various compartments.

Basis for representing RBCs as a single compartment. The RBCs have a high affinity for lead and contain nearly all of the blood lead (BPb) under most conditions. The blood concentration increases approximately linearly with intake at relatively low levels of intake but increases more slowly with high levels of intake (*17,18, 35*). It has been found that the fraction of BPb associated with plasma increases at blood lead concentrations substantially exceeding 25 μg/dl, and that there is also a nonlinear relation between lead in blood and that in urine, bone, and other tissues and fluids at such levels (*17,36–38*). As discussed later, such nonlinear behavior of lead at high levels of intake may result largely from a reduced rate of flow from plasma into RBCs as certain lead-binding components of these cells become saturat-

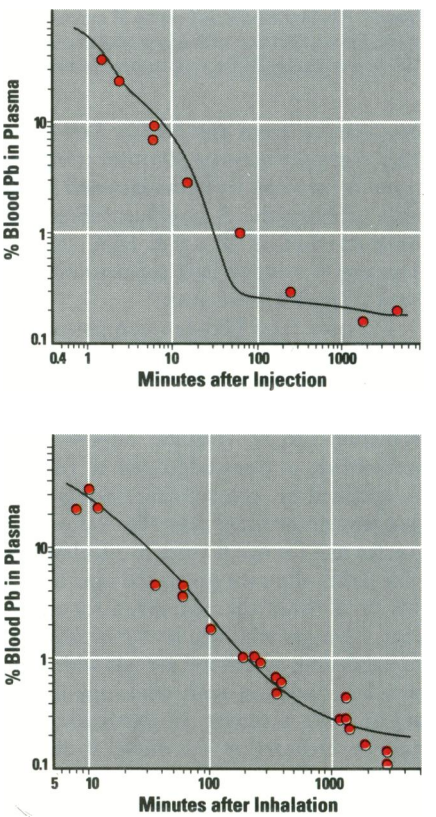


Figure 3. Model prediction (curves) and observations [circles; representing data from Chamberlain et al. (*27*)] of percent blood lead in plasma, as a function of time after administration of radiolead to adult human subjects by intravenous injection or inhalation.

ed. At least one of these components may present a moving target of sorts, in that its formation may be induced to some extent by prolonged exposure to high levels of lead (*39*).

It appears, therefore, that a fairly detailed process model of uptake and retention of lead by RBCs would require several compartments, with some being saturable and at least one having an exposure-dependent saturation level. At present, there is not sufficient quantitative information to derive transfer rates for multiple compartments within RBCs. In this model the RBCs are represented as a single compartment in exchange with diffusible plasma, but nonlinear kinetics is imposed at relatively high concentrations of lead in RBCs. That is, above a threshold concentration of lead in RBCs, the transfer rate from plasma to RBCs is assumed to decrease as the concentration of lead in RBCs increases.

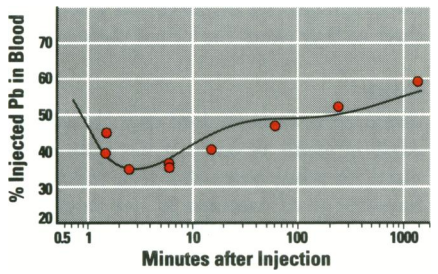


Figure 4. Model predictions (curve) and observations [circles; representing data from Chamberlain et al. (*27*)] of the blood content of radiolead as a function of time after intravenous injection into adult human subjects.

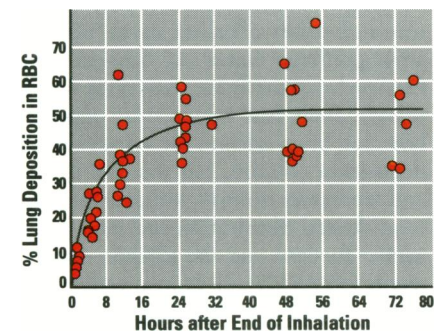


Figure 5. Model predictions (curve) and observations [circles; representing data from Hursh et al. (*42*)] of buildup of radiolead in red blood cells as a function of time after inhalation by adult human subjects.

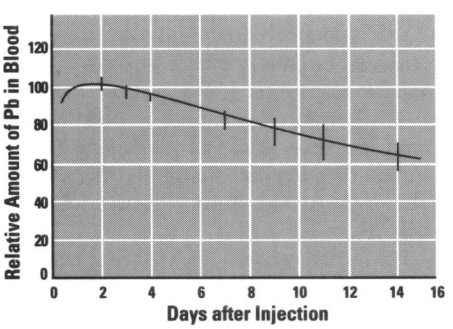


Figure 6. Model predictions (curve) and observations vertical lines; indicating range of values reported in Chamberlain et al. (*27*)] of decline of lead content of blood as a function of time after injection of radiolead into adult human subjects. Predictions and observations have been normalized to 100% at 2.5 days.

Transfer rates between diffusible plasma and RBCs. A minimum blood content of about one-third of the injected amount is reached within 2–3 min (Fig. 4), at which time roughly three-fourths of BPb resides in RBCs (Fig. 3). The RBC content then increases over a period of hours as most of the systemically distributed lead returns to plasma (*31,40,41*). By 1 day after administration of radiolead to adult humans, blood typically contains 55–60% of the injected or absorbed amount (Figs. 4 and 5) *27,28,31,32,41–45*). Over the next several weeks, lead is lost from blood with a net half-time on the order of 15–20 days (Fig. 6) (*9,27,28,32,46,47*). As indicated in Figure 7, longer net half-times and sizable intersubject variability are apparent at times remote from exposure, when the blood content may be determined as much by the rate of feedback from bone and soft tissues as by the rate of loss from RBCs.

Available data on retention of tracer lead in blood of human subjects can be reproduced reasonably well by assuming that the RBCs receive about a fourth of the lead atoms leaving diffusible plasma (more precisely, a deposition fraction of 0.24 is assigned) and return lead to diffusible plasma with a removal half-time of 5 days. Thus, for low concentrations of lead in RBCs, the transfer rate from diffusible plasma to RBCs is 0.24 × (2000/day) = 480/day. As described later, the deposition fraction for RBCs is assumed to decrease when the concentration of lead in the RBCs exceeds 60 µg/dl RBC, which corresponds to about 25 µg/dl blood.

Transfer rates between diffusible and bound plasma. The protein-bound fraction of plasma lead is not known, but it appears to be considerably larger than the diffusible fraction under steady-state conditions (*26,29,30,37,48*). After parameter values for diffusible plasma and RBCs are set, reasonable estimates of the transfer rate from diffusible plasma to protein-bound plasma and of the removal half-time from protein-bound plasma lead can be inferred from data on 1) the time-dependent division of radiolead between RBCs and plasma, 2) the steady-state division of lead between RBCs and plasma, and 3) the ultrafilterable fraction of plasma lead.

Data on healthy human subjects receiving radiolead by injection or inhalation

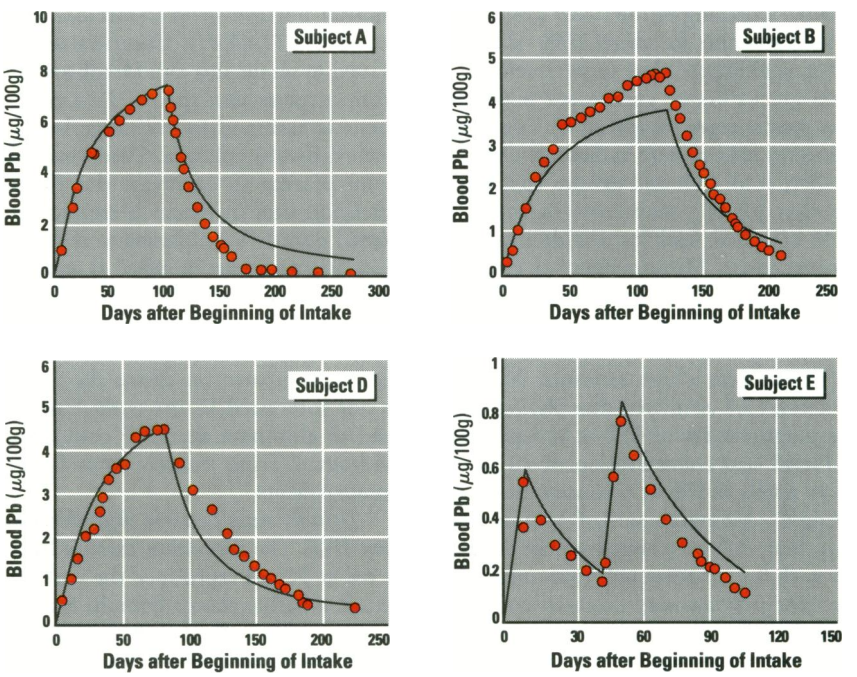


Figure 7. Model predictions (curves) and observations [circles; representing data from Rabinowitz et al. (*9*)] of lead content of blood of adult human subjects as a function of time after beginning of controlled ingestion of an isotope of lead. Ingestion periods for subjects A, B, and D were 104, 124, and 83 days, respectively; subject E ingested the lead tracer for 8 days and again on days 42–51 after the initial intake. The gastrointestinal absorption fractions assumed for subjects A, B, D, and E were 0.10, 0.07, 0.12, and 0.09, respectively, as derived by Rabinowitz and co-workers (*9*) and adjusted by Chamberlain et al. (*27*).

indicate that the RBCs contain 95–99% of the blood content of radiolead at 0.5–1 hr after injection (*31,33*), more than 99% at 3 hr after injection (*31*), more than 99.5% at 10 hr or more after injection or inhalation (*27*), and about 99.8% at 50–100 hr after injection (*28*). Experimental determinations of the time-dependent division of lead between RBCs and plasma in human subjects are shown in Figure 3 (*27*). Such findings for humans are reasonably consistent with modern data on laboratory animals. For example, more than 99% of ^{210}Pb in blood was associated with RBCs by 1 hr after injection of this isotope into beagles (*49*); about 99.8% of ^{210}Pb in blood was found in RBCs of adult monkeys at 96 hr after oral intake of this isotope (*50*); and nearly 99.8% of ^{210}Pb in blood was associated with RBCs by 1 day after injection into rabbits (*51*). In rats, plasma may contain as much as 2% of BPb, even at low blood lead levels (*20,52*).

The division of lead between RBCs and plasma of chronically exposed humans or laboratory animals has not been clearly established, mainly because of the difficulty in measuring the typically low concentration in plasma and the possibility of cross-contamination from RBCs (*27,53*). Another complicating factor is that (as discussed later) there is a nonlinear relationship between the plasma lead and blood lead concentrations, at least when the latter greatly exceeds 25 µg/dl (*17,18, 36–38*). According to the ICRP (*54*), plasma lead accounts for about 10% of blood lead at equilibrium, but more recent estimates are in better agreement with the lower percentages suggested by relatively short-term studies with radiolead. Data of Cavalleri et al. (*55*) and deSilva (*53*) indicate that plasma may contain roughly 1–2% of blood lead for a wide range of exposure levels. Measurements of Everson and Patterson (*56*) suggest that plasma contained only about 0.01% of BPb in a typically exposed person and about 0.15% in a person with a high exposure. Manton and Cook (*37*) estimated that plasma contains roughly 0.2% of BPb at an equilibrium blood lead concentration of 10 µg/dl and as much as 2% at a concentration of 100 µg/dl. Measurements of Minoia and co-workers (*57*) on a large number of subjects with no occupational exposures indicate that plasma may contain roughly 0.1% of BPb. The present model is designed to yield an equilibrium plasma lead content of 0.2% of BPb for low levels of lead intake (but higher percentages for elevated intakes), since this value is suggested by studies on humans administered radiolead and is reasonably consistent with recent measurements of stable lead in humans.

Results of renal clearance studies on dogs receiving either a single injection or continuous infusion of radiolead suggest a gradual decrease with time in the ultrafilterable portion of plasma lead (*26*). These results, together with renal clearance data on chronically exposed human subjects (*37,48*), indicate that the ultrafilterable portion of plasma lead during continuous intake may be in the range 5–30%, with perhaps 15% being typical.

Transfer rates between diffusible and bound plasma lead were set for agreement with 1) data on the early division of radiolead between plasma and RBCs, 2) experimental determinations of urinary clearance of plasma lead (discussed later), 3) the estimate that plasma lead represents 0.2% of BPb at equilibrium, and 4) the estimate that 15% of plasma lead is ultrafilterable at equilibrium. The deposition fraction in the bound plasma compartment is set at 0.0004, yielding a transfer rate of 0.0004 × (2000/day) = 0.8/day from diffusible to bound plasma. The assigned removal half-time from bound to diffusible plasma is 5 days, which is of the same order as the half-life of plasma proteins (*58*).

Basis for the EVF compartment. After intravenous injection of lead, the blood concentration is rapidly reduced by transfer from plasma to other extracellular fluids, but the simultaneous transfer from plasma to RBCs reverses the gradient within a few minutes and brings back a substantial portion of extravascular lead to blood (*28,31,40,41*). Compartment EVF is used to model this rapid feedback of lead from extravascular spaces. This compartment is assumed to exchange lead only with diffusible plasma. Lead that moves from plasma to extravascular fluids to retention sites in tissues is treated as if it passed directly from plasma to those retention sites and thus, in effect, is regarded as passing instantaneously through the EVF (Fig. 2). This treatment of the EVF as a satellite compartment rather than a central feeding compartment allows the user who is not interested in the early kinetics of lead to eliminate the EVF compartment without altering transfer rates for other compartments.

Transfer rates between diffusible plasma and EVF. The deposition fraction for EVF is set at 0.5 to reproduce the early rapid return of lead to plasma from the extravascular spaces. Thus, the transfer rate from diffusible plasma to EVF is 0.5 x (2000/day) = 1000/day. The transfer rate from EVF back to diffusible plasma is assumed to be one-third as great, or 333.3/day; this is derived from the postulate that the EVF compartment contains three times as much lead as diffusible plasma at equilibrium, which is suggested by kinetic analysis of plasma disappearance curves for isotopes of the alkaline earth elements. For example, Hart and Spencer (*34*) estimated from measurements on humans injected with radiocalcium that the volume of the rapidly exchanging extravascular fluids is about 3 (2.4–4.5) times the volume of the plasma pool. Similarly, Harrison and co-workers (*59*) concluded from measurements on an adult male subject that intravenously injected radioisotopes of calcium, strontium, barium, and radium were rapidly dispersed into an extravascular pool about three to four times the size of plasma.

Bone

Similarities between lead and the alkaline earth elements in bone. It has been recognized for many years that lead follows the movement of calcium in the body to a large extent and that physiologic regulators of calcium metabolism usually affect the behavior of lead in a qualitatively similar fashion (*60–64*). A particularly close resemblance between these two elements has been observed with regard to their behavior in bone. It has been found that lead competes with calcium for deposition in bone and distributes similarly to calcium and other alkaline earth elements among different bones and between trabecular and cortical bone structures (*49,60–62,65*). Bone lead may remain more mobile than bone calcium for some time after deposition (*66,67*), but data on humans and laboratory animals indicate that long-term skeletal distribution and retention are similar for lead and the alkaline earth elements (*49,68–71*). In human cadavers, the lead concentration was closely related to the calcium concentration in bone biopsy samples, despite the nonuniform distribution of lead found in the skeleton (*72*). Lead has been used frequently as a marker of bone growth and osteon formation, and a close resemblance in the patterns of deposition of lead and calcium in forming osteons has been demonstrated (*73–77*). Lead is incorporated into the crystalline structure of bone, where it replaces calcium ions at some sites (*78–81*). Burial of lead beneath surfaces in regions of bone formation has been observed, and there is evidence that lead is eventually distributed throughout the bone volume (*73–77, 82–86*).

Similarities between lead and calcium are also evident with regard to bone cell metabolism. A significant fraction of cellular lead in bone is rapidly exchangeable and is modulated by the same ions and hormones that regulate bone calcium metabolism (*87–89*). However, high concentrations of lead in bone leads to damage to bone cells and interference with bone remodeling (*90*).

Structure of the bone model. Based on the qualitatively similar behaviors of lead and the alkaline earth elements with regard to bone, a bone model structure originally developed for application to the alkaline earth elements (*22,91*) is applied here to lead. As far as practical, parameter values are developed on the basis of lead-specific data, but appeal is made to the alkaline earth analogy wherever data on lead are lacking.

The model structure is an updated version of the long-standing alkaline earth model for adult humans described in ICRP Publication 20 (*92*). This new version has been adopted by the ICRP for consideration of the age-specific biokinetics of calciumlike elements. As in the ICRP's earlier model (*92*) for alkaline earth elements: 1) bone is divided into four primary parts: cortical surface, cortical volume, trabecular surface, and trabecular volume; 2) the rapidly exchangeable material in bone is assumed to reside on bone surfaces, meaning endosteal and periosteal surfaces of cortical bone, surfaces of haversian and Volkmann canals, surfaces of resorption cavities, and surfaces of trabecular bone. Bone surfaces do not include the surfaces of lacunae or canaliculi and should not be confused with the surfaces of the sub-microscopic bone crystals; 3) the more slowly exchangeable material in bone is assumed to reside in bone volume; 4) long-term loss from bone is associated primarily with bone resorption. In contrast to the ICRP's earlier model for alkaline earth elements: 1) redeposition of material removed from bone compartments is treated explicitly and 2) material is assumed to be removed from all bone compartments by first-order processes.

The ICRP's earlier alkaline earth model is a catenary (non-recycling) model involving a power-function component that accounts for most of the biological removal from bone volume occurring from a few weeks to several months after injection (*92*). This intermediate-term loss from bone is generally ascribed to "diffusion" of material into osteons and/or ionic exchange of a portion of the element in deep bone with shallow bone pools or plasma calcium and has been incorporated into some biokinetic models for lead (*15,20*). Actually, the processes giving rise to intermediate-term loss from bone have not been clearly established, either for lead or for the alkaline earth elements. For lead, much of the loss from bone occurring from a few days to a year or more after exposure might result in part from the bone diffusion process generally hypothesized and in part from other processes, such as turnover of lead-binding components of the organic matrix of bone (*93*) or gradual release of lead from cellular components of bone.

Whatever the processes, the existence of intermediate-term loss of lead from bone is indicated by data on laboratory animals injected with radiolead (*15,20,49, 71,82,94*). Also, the hypothesis that a substantial portion of bone lead remains exchangeable for some time after exposure is consistent with data on persons who have received chelation therapy after exposure to lead (*95*), although it must be considered that high concentrations of lead may have changed the kinetics of lead in bone.

In the present model, cortical and trabecular bone volume are each viewed as consisting of two pools, referred to as the exchangeable and nonexchangeable pools (Fig. 1). The exchangeable bone volume pool is identified with intermediate-term loss from bone, meaning loss not associated with rapid exchange with plasma or slow loss by bone resorption. Calciumlike elements moving from bone surfaces to bone volume are assumed to enter the exchangeable pool and to leave this pool with an element-specific half-time (a few weeks or months). Part of the material leaving exchangeable bone volume is assumed to return to rapidly exchanging bone surfaces and part is assigned to the nonexchangeable bone volume, from which it is assumed to be removed to plasma only by bone resorption. The rate of removal from nonexchangeable bone volume is equated with the rate of bone turnover and is independent of the calciumlike element considered. The parameter values assigned to exchangeable bone volume and bone surfaces are assumed to include any effects of bone resorption.

The assumptions that 1) bone lead is rapidly exchangeable if and only if it resides on bone surfaces, 2) bone volume is in exchange with bone surfaces and not plasma, and 3) all lead reaching bone volume is initially available for exchange are, at best, only partially accurate. The trilayered model of bone is intended only to approximate the net result of the various processes involved in the time-dependent uptake and removal of lead from bone, using first-order kinetics and a minimal number of compartments. This layered structure is consistent with a qualitative model proposed by Rabinowitz (*95*), who suggested that not all bone lead is equally exchangeable with blood but has varying degrees of accessibility until penetrating the crystal surface, after which it becomes firmly buried and must await osteoclastic turnover.

Rates of uptake and loss by bone surfaces. The net rate of exchange between diffusible plasma and rapidly exchanging regions of bone (assumed to be at the bone surfaces) and the amount of lead initially retained in bone can be inferred from generally consistent data on healthy adult male humans (*28*), baboons (*82*), and beagles (*49*) injected with radiolead. These data indicate that the adult skeleton accumulates about 10–15% of intravenously injected lead within a few hours. This rapid uptake may be followed by a decline in the bone content over the first day or two after injection and then a gradual increase over a period of weeks as lead returns from RBCs and soft tissues to plasma and accumulates in regions of bone with slower loss. By 3–4 weeks after injection, bone contains roughly 25% of the administered amount (Fig. 8). These data can be reproduced reasonably well if it is assumed that 1) the deposition fraction on all bone surfaces is 0.08. (Derivation of transfer rates from diffusible plasma to the individual bone surface compartments requires additional information, discussed below, on the initial division of lead between trabecular and cortical bone); 2) lead is removed from each bone surface compartment at a rate of 1/day, with half of the removed lead returning to diffusible plasma and half migrating to sites in bone with longer retention (exchangeable bone volume). Thus, the transfer rate from trabecular or cortical bone surface to diffusible plasma is 0.5/day, and the transfer rate from trabecular or cortical bone surface to the corresponding exchangeable bone volume compartment is also 0.5/day.

Injection data on a variety of animal species (*60,62,82,96*) indicate that the concentration of lead is initially much higher in trabecular bone than in cortical bone. McLean and co-workers (*62*) found that the concentration of radioactive lead in trabecular bone of dogs was at least five times higher than that in cortical bone soon after injection. This seems consistent with limited biopsy data on human subjects ingesting a lead isotope tracer over a period of months (Table 2), when it is considered that the samples of cortical bone were almost entirely bone tissue, and the trabecular samples probably contained about twice as much soft material as bone tissue, by mass (M. Rabinowitz, personal communication; *18*). Since the biopsies were taken more than 3 months after the beginning of exposure, some redistribution of bone lead is likely to have occurred.

The initial division of lead between trabecular and cortical bone appears to be similar to that of the alkaline earth elements [compare, for example, results of McLean et al. (*62*) for lead in dogs with results of Norrdin and Arnold (*65*) for calcium in dogs]. As assumed earlier for the alkaline earth elements (*91,97*), the rate of transfer of lead from diffusible plasma to trabecular and cortical bone surfaces is

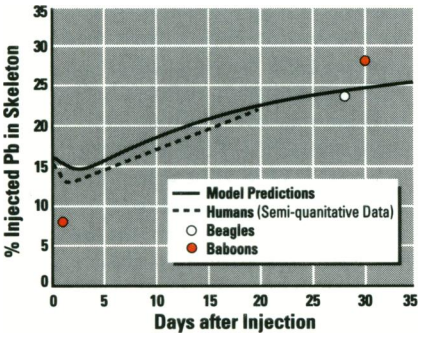


Figure 8. Model predictions and observations of the lead content of the adult skeleton as a function of time after intravenous injection. The observations for humans are indirect estimates for subjects intravenously injected with ^{203}Pb, derived by consideration of material balance, together with external measurements over the feet (*28*). The data point for beagles is from Lloyd et al. (*49*), and data for baboons are from Cohen et al. (*82*).

assumed to be proportional to the calcium addition rate of the given bone type. Since there is roughly four times as much cortical bone as trabecular bone by mass in the adult human (*54*), and the rate of addition of calcium per gram bone is on the order of five to six times higher in trabecular than cortical bone as an average over all adult ages (*91,97*), the rate of transfer of lead from diffusible plasma to trabecular surfaces is estimated to be 1.25 (5/4) times higher than that to cortical surfaces in the adult. Since the deposition fraction for all bone surfaces of the adult is estimated as 0.08, the transfer rate from diffusible plasma to trabecular bone surfaces is

$$(1.25/2.25) \times 0.08 \times (2000/\text{day}) = 88.9/\text{day}$$

and the transfer rate from diffusible plasma to cortical bone surfaces is

$$(1.00/2.25) \times 0.08 \times (2000/\text{day}) = 71.1/\text{day}.$$

Rates of loss from the exchangeable bone volume compartments. Parameter values for the exchangeable bone volume compartments are based on 1) data on retention of ^{210}Pb in whole bodies and bones of baboons (*82*) and beagles (*15,49, 94*); 2) the fraction of total-body lead in bone of chronically exposed humans; 3) apparent similarities between lead and radium with regard to intermediate- and long-term retention in bone; and 4) the assumption that the transfer rates to and from exchangeable bone volume are the same for trabecular as for cortical bone. The data on baboons and beagles suggest that most of the peak content of lead in bone is removed from the body within a few months. Data on humans chronically exposed to lead, summarized in a later section, are consistent with the assumption that a relatively small portion (on the order of 20%) of lead entering bone volume is retained over an extended period. The inferred pattern of translocation of lead from exchangeable bone volume is broadly similar to that described earlier for radium (*91*). By analogy with radium it is assumed that the removal half-time of lead from exchangeable bone volume is 30 days, that 20% of lead leaving exchangeable bone volume moves to nonexchangeable bone volume, and that 80% returns to bone surfaces. Thus, the transfer rate from the exchangeable to the nonexchangeable bone volume compartment of either trabecular or cortical bone is $0.2 \times 0.693/(30 \text{ days}) = 0.00462/\text{day}$ and from exchangeable bone volume to bone surface is $0.8 \times 0.693/(30 \text{ days}) = 0.0185/\text{day}$.

Rates of loss from nonexchangeable bone compartments. Studies of beagles injected with radioisotopes of lead, radium, or strontium indicate that skeletal retention is similar for these elements, particularly after a few weeks, and that their rate of removal from the skeleton after a few months may be largely controlled by the rate of bone resorption (*49,71*). As in an earlier model for the alkaline earth elements (*22,91*), it is assumed that the rate of removal of lead from nonexchangeable bone volume is the same as the rate of bone turnover and that lead leaving nonexchangeable bone volume enters diffusible plasma. The age-specific bone turnover rates given in Table 1 are those developed in an earlier paper (*97*) and adopted by the ICRP (*21*). These values are based on histomorphometric measurements on human subjects and studies of retention of certain bone-seeking radionuclides in human subjects. Most histomorphometric measurements are on ribs and iliac crest, but there are also a few measurements for various long bones. It is assumed that there are no differences in turnover rates of cortical and trabecular bone early in life but that differences gradually appear during childhood and eventually grow to about a factor of 6 in the mature adult. Differences with age in bone turnover during adulthood (*23,24, 97*) are not addressed here.

Table 2. Measurements and model predictions of the concentration (μg/g) of lead in biopsied iliac bone from human subjects ingesting a lead isotope tracer over a period of months[a]

	Observed/this model	
Bone type	Subject A day 116	Subject B day 105
Trabecular	0.075/0.097	0.045/0.060
Cortical	0.049/0.058	0.054/0.036

[a]Data are from Rabinowitz et al. (*9*). The concentrations are expressed on a fresh-weight basis. The observations indicate considerably greater concentrations of lead in trabecular than cortical bone tissue at 105–116 days from the beginning of exposure because trabecular biopsy samples generally contain more soft material than bone tissue by mass. Model predictions are based on the assumption that the cortical samples represent 4000 g of bone tissue and the trabecular samples represent 1000 g of bone tissue plus 2000 g of soft material.

Several authors have attempted to identify a single, long-term turnover rate of lead in the adult human skeleton. Estimates have been based on animal studies, the rate of bone remodeling, balance considerations regarding ^{210}Pb or stable lead, the decline of BPb after the end of occupational exposure, and *in vivo* measurements of the decline of ^{210}Pb or stable lead in bone after elevated exposures (*46,98–107*). Estimates have ranged from about 0.007/year to about 0.15/year.

Cohen and co-workers (*107*) used *in vivo* measurements over the skull and urinary excretion measurements to estimate the rate of decline of ^{210}Pb (radiological $T_{1/2}$ = 22.3 years) in a subject contaminated with this radionuclide 33 years before the initial measurements in 1980. They estimated from *in vivo* measurements that the total-body content was 9.55 kBq in 1980 and 5.88 kBq in 1990. If exponential decline is assumed, these initial and final estimates would indicate a biological removal rate of 0.017/year. If three *in vivo* measurements made between 1980 and 1990 are included and a best exponential fit to the five measurements is derived, a biological removal rate of only 0.007/year is obtained. If it is assumed that urinary excretion represents 55–60% of total excretion of lead at times remote from exposure (see the section on excretion), the urinary excretion measurements (taken in 1990) indicate a biological removal rate of 0.021–0.023/year. The present model predicts that a total-body burden of 9.55 kBq of ^{210}Pb remaining after an acute intake 33 years earlier would decline to 5.15 kBq after 10 more years, and that the biological removal rate from the total body at 43 years would be about 0.027/year (if model predictions for 42-44 years are approximated by a single exponential function).

Christoffersson and co-workers (*108*) used *in vivo* X-ray fluorescence to measure the decline of lead in finger bone in former lead workers. For eight subjects followed for up to 5 years, a biological half-time of 6.7 (range 3–15) years was estimated. In a second group of six persons followed from year 7 to year 13 after finishing lead work, a half-time of 8.2 (range 2–∞) years was estimated. There was generally good agreement between the estimated decline of lead in finger bone and the decline in blood of these subjects (*106,108*). Based on these

data and additional measurements of lead in bone biopsies (vertebrae), blood, and urine of present or former lead workers, Skerfving et al. (*106*) concluded that the skeletal lead pool is not kinetically homogeneous, that turnover of lead is faster in the mainly trabecular vertebrae than in the mainly compact finger bone, and that the "average over-all half-time is probably 5–10 years."

Only broad comparisons between model predictions and findings of Christoffersson, Skerfving, and co-workers can be made due to the paucity of information on the lead exposures experienced by the subjects. The model does not predict a single biological half-time for bone after an extended elevated exposure; rather, the rate of loss from the total skeleton is predicted to decrease gradually as the fraction of bone lead in nonexchangeable cortical bone increases. Also, the rate of decline depends somewhat on the pattern and duration of the exposure, which affect the distribution of bone lead at the end of exposure. For presumably realistic occupational exposure scenarios, the predicted decline in total bone lead after the end of exposure corresponds to a half-time on the order of 10–12 years during the first few years after exposure and roughly 25 years at 25–30 years after exposure.

Liver: Model Structure and Transfer Rates

The liver and kidneys are treated separately from other soft tissues because of their importance as excretion pathways for lead and because they show substantially higher concentrations of lead than most soft tissues.

Data on injected lead in human subjects (*28*), baboons (*82*), and beagles (*49*) indicate that the liver rapidly accumulates 10–15% of systemic lead and loses much of this within a few weeks. In chronically exposed adult humans, the liver may contain about 2–3% of total-body lead, and the blood-to-liver lead concentration ratio is about 0.2 (54,109–115). Part of the loss of lead from liver can be accounted for by biliary secretion into the gastrointestinal contents (*9,116*), but return of a considerable portion of liver lead to blood must also be postulated due to the limited losses of lead in feces. Since the level of biliary secretion of metals varies considerably from one species to another (*117*), quantitative information on biliary secretion of lead by laboratory animals (particularly rodents) is of limited value for present purposes.

In this model the liver is viewed as consisting of two compartments. A compartment with relatively high uptake from plasma and a relatively short removal half-time (several days) is needed to help reproduce the pattern of uptake and decline of lead observed in human subjects, baboons, and beagles during the first few weeks after intravenous injection. An additional liver compartment with much smaller uptake but with gradual build-up of lead over a period of years is then needed to reproduce the blood-to-liver concentration ratio determined from data on chronically exposed human subjects. The two liver compartments are referred to as liver 1 and liver 2.

Available data on hepatic uptake and retention of lead in humans and laboratory animals and on biliary secretion of lead in humans can be reproduced reasonably well with this two-compartment model and the following assumptions: 1) of lead leaving diffusible plasma, 4% deposits in liver 1. Thus, the transfer rate from diffusible plasma to liver 1 is $0.04 \times (2000/\text{day}) = 80/\text{day}$; 2) the removal half-time from liver 1 is 10 days. Of lead leaving liver 1, 10% moves to the long-term retention compartment (liver 2), 45% enters the contents of the small intestine via biliary secretion, and 45% returns to diffusible plasma. Thus, the transfer rate from liver 1 to liver 2, for example, is $0.1 \times 0.693/(10\ \text{days}) = 0.00693/\text{day}$. Lead entering the contents of the small intestine in liver bile is assumed to follow the same kinetics as ingested lead (see appendix); 3) the removal half-time from liver 2 is 1 year. All lead leaving liver 2 is assumed to return to diffusible plasma.

Model predictions are reasonably consistent with data on chronically exposed adult humans indicating that the liver may contain roughly 2–3% of total-body lead. Also, the model predicts a blood-to-liver lead concentration ratio of 0.2 for the chronically exposed adult, in agreement with the data on adult humans. Model predictions of the adult liver content of lead during the first several weeks after injection are compared in Figure 9 with data on human subjects, baboons, and beagles injected with radiolead. The observations for human subjects indicated in Figure 9 are only semiquantitative estimates based on external measurements. The liver content in baboons or beagles at 1–2 months is expected to provide only a lower-bound estimate for humans because the lead contents in the total body and blood (and presumably all compartments with relatively high turnover rates) decline faster in those animals than in humans (*28,49,82*).

Kidneys: Model Structure and Transfer Rates

Results of studies on dogs and rodents indicate that the kidneys may accumulate as much as 15–20% of intravenously injected radiolead within the first 1–2 hr, that the preponderance of the deposited activity represents filtered lead, and that a substantial portion of the early accumulation is reabsorbed or lost in urine within a few hours (*118–120*). In rats, the kidneys contained roughly 10% of the intravenously injected amount after 1 day but less than 2% after 9 days (*82*). In baboons receiving radiolead by intravenous injection, the kidneys contained roughly 4% of the administered amount after 1 day, 0.6% after 30 days, and 0.1% after 60 days (*82*). Comparison of the decline of renal and hepatic activity over the first two months in these baboons indicate a half-time in the kidneys that would be roughly one-half of that in the liver, if each of these organs were considered as a single compartment. This agrees with estimates of Mallon (*13*) for baboons exposed to lead by daily ingestion over a period of a few months. In dogs receiving ^{210}Pb by intravenous injection, the kidneys contained about 0.5% of the administered activity at 1 month (49).

In this model the kidneys are viewed as consisting of two compartments, one with relatively high deposition but short retention of lead and one with relatively low uptake but long retention. These compartments are referred to as the "urinary path" (UP) and "other kidney tissue" (OKT), respectively. Both are assumed to receive lead from diffusible plasma. Material removed from UP moves to the urinary bladder contents, and that removed from OKT returns to diffusible plasma. Compartment UP is needed to reproduce an early rapid buildup and fairly fast (days) decline of lead in the kidneys as indicated by data on laboratory animals, as well as the early (2-week) pattern of decline of lead in urine as indicated by data on human subjects injected with radiolead. Compartment OKT is needed to repro-

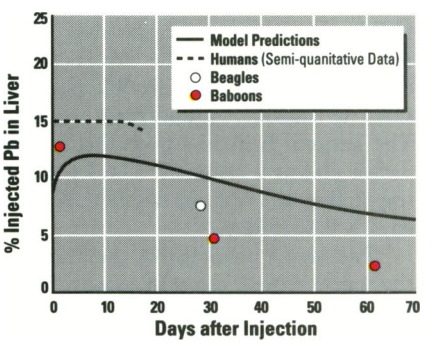


Figure 9. Model predictions and observations of the lead content of the adult liver as a function of time after intravenous injection. The observation curve for humans is based on external measurements on adult human subjects intravenously injected with ^{203}Pb (*28*). The data point for beagles is from Lloyd et al. (*49*), and data for baboons are from Cohen et al. (*82*).

duce blood-to-kidney and liver-to-kidney lead concentration ratios observed in chronically exposed persons. No attempt is made to quantify separately the rates of glomerular filtration, tubular absorption, and tubular secretion, all of which apparently occur for lead (*26,119,121*). Rather, movement of lead from diffusible plasma into the kidney compartments and urinary bladder contents is described only in terms of the net result of these three processes.

The parameter values for the UP compartment of the kidneys were based largely on the data for laboratory animals summarized above but were adjusted for consistency with time-dependent urinary excretion rates observed in human subjects acutely exposed to radiolead (see the discussion of the parameter values describing urinary excretion). No attempt was made to reproduce the rapid accumulation and decline of lead in the kidneys that occurs in the first hour or two after injection.

It is assumed that 2% of lead leaving diffusible plasma deposits in the urinary path compartment, UP, yielding a transfer rate from diffusible plasma to UP of 0.02 × (2000/day) = 40/day. The removal half-time from UP to the urinary bladder contents is assumed to be 5 days, corresponding to a transfer rate of 0.693/(5 days) = 0.139/day.

After the parameter values for the urinary path compartment were selected, those describing uptake and removal by the OKT compartment (which represents tenacious retention in the kidneys) were set for consistency with estimated relative lead contents in liver and kidneys of human subjects chronically exposed to lead. That is, parameter values for this compartment were set to account for the difference between the total kidney content and the content of the urinary path compartment during chronic exposure.

It is assumed that the OKT compartment receives 0.02% of lead leaving diffusible plasma (amounting to about 1% of the total deposition in the kidneys). Thus, the transfer rate from diffusible plasma to OKT is 0.0002 × (2000/day) = 0.4/day. The removal half-time from OKT to diffusible plasma is assumed to be 1 year, corresponding to a transfer rate of 0.693/(365 days) = 0.0019/day.

The model predicts that the kidneys of the adult would contain almost 5% of intravenously injected lead after 1 day, almost 2% after 1 month, and almost 1% after 2 months. The model was designed to overestimate observed kidney contents in baboons and beagles at 1–2 months because the content of lead in blood and the total body decline faster in those animals than in humans.

Brain: Model Structure and Transfer Rates

The brain is considered explicitly in this model because of its high sensitivity to lead as a chemical toxin. Lead is distributed unevenly in the brain, with the distribution depending to some extent on the level of exposure. At low levels, the lead concentration in different regions of the human brain is significantly correlated with the potassium concentration, indicating that lead is mostly accumulated in cell-rich parts of the brain such as the hippocampus (*122–124*). As with other types of cells, lead entering brain cells apparently is taken up rapidly by mitochondria, accumulating predominantly in those regions where calcium localizes (*87*). At very high levels, lead gains access to neural tissue following breakdown of the blood–brain barrier (*124*). In cases of lead poisoning in young children, the lead concentration of the brain becomes extremely high and may approach or even exceed that of the liver and kidney (*125,126*).

It appears, therefore, that a fairly detailed model of the behavior of lead in the brain would require multiple compartments and consideration of nonlinear kinetics. Due to limitations in kinetic data, however, the brain is treated here as a single compartment that exchanges lead slowly with diffusible plasma, and linear kinetics is assumed.

Data on baboons, dogs, and rodents indicate that the brain has low uptake but tenacious retention of lead (*49,82,120*). In young adult female baboons intravenously injected with ^{210}Pb, the brain contained about 0.04% of the administered lead at 1 day but continued to accumulate activity released by other organs, showing about 0.07% after 30 days and 0.08% after 60 days (82). In beagles, the brain contained 0.04% of injected ^{210}Pb at 1 month after injection and <0.003% at 3-4 years.

An assumed deposition fraction for brain of 0.00015 [corresponding to a transfer rate from diffusible plasma to brain of 0.00015 × (2000/day) = 0.3/day] and a removal half-time of 2 years yield predictions that are reasonably consistent with injection data for large laboratory animals and with autopsy data for occupationally as well as environmentally exposed adult humans. The model predicts that the adult brain contains 0.04% of administered lead at 1 day and 0.13% at 60 days after injection and gradually increases to a peak content of 0.15% at 6 months.

Other Soft Tissues: Model Structure and Transfer Rates

The remaining soft tissues, consisting of skeletal muscle, fat, skin, and a variety of small organs and tissues, represent most of the body's mass but only a small percentage of its lead content in the chronically exposed adult. Data on laboratory animals administered radiolead indicate that initial deposits of lead in skeletal muscle and other massive soft tissues are largely cleared by 1 day after administration and that these tissues probably account for no more than 3–4% of the absorbed amount after that time (*49,52,82,94,119,127*). There are indications, however, that small amounts are tenaciously retained in skeletal muscle, aorta, and perhaps other soft tissues (*49,82*).

In this model the other soft tissues are assumed to consist of three compartments, ST0, ST1, and ST2, representing a wide range of turnover rates. These compartments are based primarily on kinetic considerations and cannot be given precise anatomical definitions.

Compartment ST0 is assigned a high turnover rate and, together with bone surfaces, accounts for most of the feedback from extravascular spaces to plasma occurring from about 30 min (when compartment EVF is virtually depleted) to a few days after acute intake. Based on the blood "reappearance" curve for lead during the first day and considerations of mass balance of the deposition fractions in different organs, it is assumed that ST0 receives almost 9% (precisely, 8.875% to achieve mass balance of deposition fractions) of lead leaving diffusible plasma and loses lead to diffusible plasma with a removal half-time of 8 hr. Thus, the transfer rate from diffusible plasma to ST0 is 0.08875 × (2000/day) = 177.5/day and from ST0 to diffusible plasma is 0.693/(0.333 day) = 2.08/day.

In beagles injected with ^{210}Pb, soft tissues other than liver, kidneys, and brain contained about 3% of the injected amount at 28 days and less than 0.2% at 1100 days (*49,94*). Most of the other soft tissue content at 28 days was found in pelt. In this model, compartment ST1 is used to depict such intermediate-term loss (i.e., a few weeks or months) from other soft tissues and also serves as the source of loss of lead from the body in substances other than urine, feces, and sweat (e.g., hair, nails, and desquamated skin). The deposition fraction for ST1, the total removal half-time from ST1 to diffusible plasma and excreta, and the division of outflow between diffusible plasma and excreta were chosen for broad consistency with data on intermediate-term retention of lead in soft tissues of laboratory animals and data on the rate of loss of lead in hair, nails, and skin of human subjects (9). It is assumed that ST1 receives 0.5% of lead leaving diffusible plasma. The total removal half-time from ST1 is assumed to be 100 days, with

60% of the outflow returning to diffusible plasma and 40% lost in hair, nails, and desquamated skin. Thus, the transfer rate from diffusible plasma to ST1 is 0.005 × (2000/day) = 10/day, the transfer rate from ST1 to diffusible plasma is 0.6 × 0.693/(100 days) = 0.00416/day, and the transfer rate from ST1 to excreta is 0.4 × 0.693/(100 days) = 0.00277/day.

Compartment ST2 represents tenacious retention of a small amount of lead in soft tissues and is used to account for most of the lead in massive soft tissues of chronically exposed humans. To avoid a gross overestimate of data for beagles injected with ^{210}Pb, it must be assumed that no more than 0.1% of the injected amount is deposited in a soft-tissue compartment with a retention time of years. Then, in order for compartment ST2 to gradually accumulate the level of lead indicated by autopsy data on chronically exposed humans, it must be assumed that the removal half-time from compartment ST2 is at least 5–10 years. It is assumed here that compartment ST2 receives 0.1% of outflow from diffusible plasma and returns lead to diffusible plasma with a removal half-time of 5 years. The transfer rate from diffusible plasma to ST2 is 0.001 × (2000/day) = 2/day and the transfer rate from ST2 to diffusible plasma is 0.693/(1825 days) = 0.00038/day.

The model predicts that the three other soft tissues, ST0, ST1, and ST2 combined, contain 6% of intravenously injected lead at 1 day, 4% at 1 month, and less than 1% at 3 years after injection. As with the liver and kidneys, the model was designed to yield reasonable consistency with the data on chronically exposed humans, and the injection data on baboons and beagles were assumed to provide lower-bound estimates for humans.

Excretion: Model Structure and Transfer Rates

Excretion of lead is divided into four pathways: urinary excretion, fecal excretion, sweat, and all other excretion pathways combined (mainly hair, nails, and desquamated skin). It is assumed that a portion of lead entering the urinary bladder passes directly from diffusible plasma to the urinary bladder contents and the rest is released to the bladder contents after temporary retention in the renal tubules (compartment UP). Lead in feces is assumed to originate from two sources: biliary secretion from the liver contents (liver 1) into the contents of the small intestine and secretion from all other sources (assumed to be diffusible plasma in this model) into the contents of the small intestine. It is assumed that the absorption fraction for lead entering the small intestine in liver

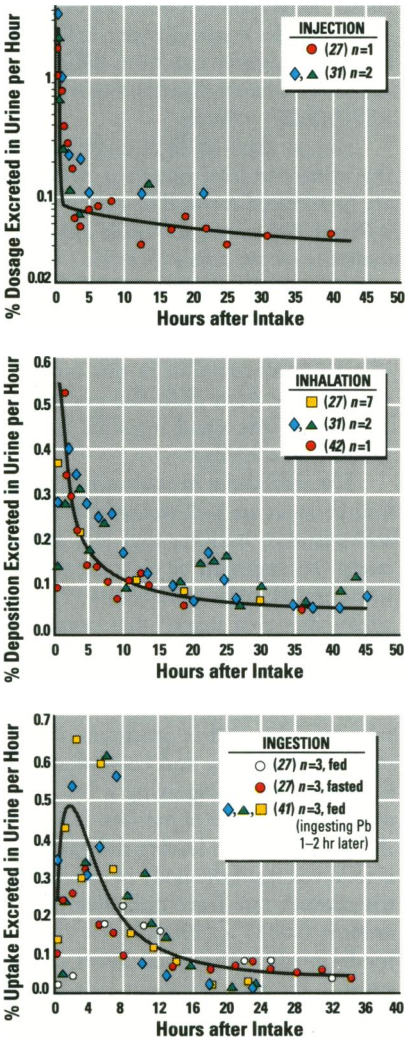


Figure 10. Model predictions (curves) and observations (symbols) of the rate of urinary excretion of radiolead at early times after administration to adult human subjects. Sources of data are indicated.

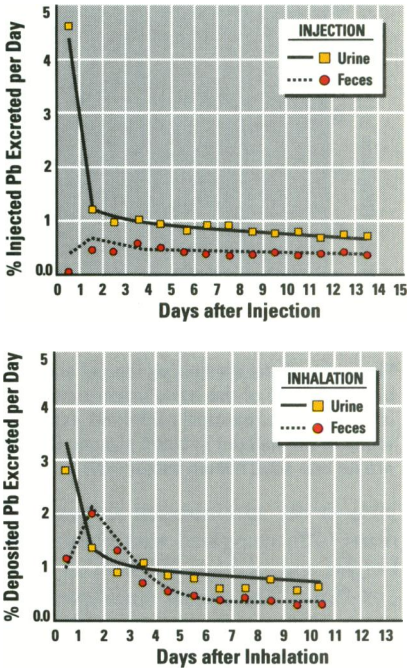


Figure 11. Model predictions (curves) and observations of the rates of urinary and fecal excretion of radiolead at early times after administration to adult human subjects. Urinary excretion data point for day 1 after injection is subject-weighted mean of central values determined in Chamberlain et al. (*27*) (6 subjects, mean 3.7%), Booker et al. (*31*) (2 subjects, mean 5%), Campbell et al. (*33*) (2 subjects, mean 7.6%), Hursh et al. (*41*) (2 subjects, mean 4.2%), and Hursh and Mercer (*44*) (4 subjects, mean 4.6%). Urinary excretion data point for day 1 after inhalation is subject-weighted mean of central values determined in (*27*) (12 subjects, mean 2.7%), (*31*) 2 subjects, mean 4.1%), Hursh et al. (*42*) (10 subjects, mean 2.9%), and (*44*) (4 subjects, mean 2.2%). Fecal excretion data point for day 1 following inhalation is subject-weighted mean of central values determined in (*27*) (12 subjects, mean 0.7%) and (*42*) (median 1.7% determined from scattered data on 10 subjects). All other data points are from (*27*) and are means for 7 or fewer subjects.

bile or other secretions is the same as that for ingested lead. Lead is assumed to be transferred directly from diffusible plasma to sweat. Losses in hair, nails, and desquamated skin are represented as a transfer from soft tissue compartment ST1 to excreta.

There have been several studies of the rate of urinary and fecal excretion of lead after administration of radiolead to human subjects. It appears from the urinary excretion curve for intravenously injected lead that a few percent of administered lead moves to the urinary bladder contents with little or no delay in the kidneys (Fig. 10). Urinary excretion curves for inhaled or ingested lead reflect brief delays in absorption to blood, superimposed on the excretion curve for injected lead (Fig. 10). For comparison of model predictions with observed urinary excretion rates in humans, it is assumed that the urinary bladder is emptied completely with each voiding. For most purposes one can remove the urinary bladder compartment from the model or assume that removal from the urinary bladder contents to urine follows first-order kinetics; a removal half-time of 0.1 day seems reasonable, based on ICRP data (*54*).

Typically, 2–5% of systemic lead is excreted in urine during the first 24 hr after administration (Fig. 11) (*31*,*41*, *42*,*44*). There is little loss in feces during the first day, but the fecal-to-urinary excretion ratio is about 0.5 during days 2–14 after injection (Fig. 11) (*27*,*28*,*32*). The fecal-to-urinary excretion ratio is slightly higher (roughly 0.7–0.8) in the first 2 weeks after inhalation due to ciliary clearance and swallowing of a small portion of the lead deposited in the lungs (Fig. 11; also see appendix). Urinary plus fecal losses during the first 20 days account for about

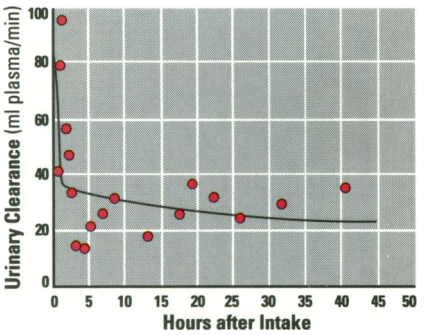


Figure 12. Model predictions (curve) and observations (circles) of the early urinary clearance of intravenously injected radiolead expressed in terms of the amount in blood plasma. Data points are for one adult human subject (*27*).

30% of the administered amount in humans (*28*), compared with about 50% in beagles and perhaps 40–50% in baboons (*18,49,82*). The present model predicts that about 27% of administered lead would be lost in urine and feces during the first 20 days after injection into the adult human.

In an adult male subject acutely exposed to ^{210}Pb 43 years earlier, daily urinary excretion was estimated to represent about 0.0035% of the current body burden as determined by *in vivo* measurements (*107*). The present model predicts that daily urinary excretion at 43 years after acute intake of lead would be 0.0049% of the current body burden.

Some authors have expressed urinary clearance of lead in terms of the amount of lead in blood plasma or serum (Fig. 12) (27,*36*), but it is more common to relate this quantity to lead in the total blood volume. In humans exposed only to environmental lead, urinary clearance of lead is typically 0.02 (range, 0.015–0.03) blood volumes per day (*9,18,57,128–131*), which is the value produced by the present model for blood lead concentrations less than about 25 µg/dl. As indicated in Figure 13 and discussed later in more detail, the daily urinary clearance may substantially exceed this value at high levels of BPb. The nonlinear relationship between lead in urine and lead in blood appears to be similar to that between plasma lead and BPb, insofar as comparisons are possible. In this model, the nonlinear relationship between urinary lead and BPb is assumed to result from the increase in diffusible plasma lead as a fraction of BPb and not from nonlinear kinetics in the kidneys.

Human data on urinary clearance of lead are reproduced reasonably well by assigning 1.5% of lead leaving diffusible plasma to the urinary bladder contents, in addition to the amount entering the bladder contents after retention in the urinary path. Recall that the latter accounts for 2% of lead leaving diffusible plasma and is assumed to be removed from the urinary path to the bladder contents with a half-time of 5 days. The transfer rate from diffusible plasma to the urinary bladder contents is 0.015 × (2000/day) = 30/day.

Human data on fecal excretion and on the urinary-to-fecal excretion ratio for lead are reproduced reasonably well by assigning 0.6% of lead leaving diffusible plasma to the contents of the small intestine. This is in addition to the amount assumed to enter the small intestine contents via biliary secretion, which accounts for about three-fourths of total fecal excretion in this model. The transfer rate from diffusible plasma to the contents of the small intestine is 0.006 × (2000/day) = 12/day.

The difficulties in measuring the loss of lead in sweat are well recognized. Results of some studies indicate that loss of lead in sweat can approach or even exceed that in urine under some conditions (*135–139*), while other data suggest that sweat is not a significant excretion pathway for lead (*27,140*). The rate of transfer from plasma to sweat used in the present model is a compromise value and is consistent with findings of Rabinowitz and co-workers (*9*) for human subjects ingesting a lead isotope tracer over a period of months. It is assumed that 0.35% of lead leaving diffusible plasma is removed from the body in sweat. That is, the transfer rate from diffusible plasma to sweat is 0.0035 × (2000/day) = 7/day. The model predicts that total losses of lead in sweat in the adult are about 10% as great as losses in urine during chronic exposure.

It is difficult to determine typical losses of lead by other excretion pathways. Hair is a well-known site of concentration of internally deposited lead, but there is also contamination of hair from external sources (*82*). As described earlier in the discussion of the other soft tissues, it is assumed that 40% of outflow from ST1 is in hair, nails, and desquamated skin, which yields a transfer rate from ST1 to excreta of 0.00277/day. Fractional transfer from ST1 to excreta was based primarily on measurements of excreta from human subjects who ingested a lead isotope tracer over a period of months (*9*), but data from less controlled studies of lead in hair or nails were also considered (*141–144*). With regard to minor excretion pathways, the model is intended only to approximate cumulative loss over an extended period. A precise treatment of the time-dependent loss of lead in hair, for example, from the time of acute intake would require a considerably more complex excretion model (*16*).

Modifications Needed to Address Nonlinear Kinetics of Lead

The concentration of lead in blood is not linearly related to the concentration in plasma or other fluids and tissues of the body, at least when the blood lead concentration substantially exceeds 25 µg/dl. This nonlinear behavior of lead is not completely understood but may result in large part from a reduced rate of flow from plasma into RBCs as certain lead-binding components of these cells become saturated (*17,18,20,39*). It has been suggested, for example, that the cell membrane may have a limited capacity for lead (*17,145*). At low levels of exposure, lead in RBCs is associated primarily with hemoglobin (*146*). The Hb A_2 component of hemoglobin, which represents only about 2% of the total hemoglobin in human RBCs, may contain one-half to two-thirds of the lead in RBCs at relatively low blood lead concentrations (*39,146*). There appears to be saturation of lead binding to Hb A_2 at low to moderate lead concentrations and an increase in the portion of lead found in the main hemoglobin component, Hb A, which may also be saturable at moderate lead concentrations (*39*). There is also evidence that an elevated blood lead concentration induces the formation of low-molecular-weight lead-binding proteins within the RBCs (*39*). The degree of synthesis of this protective lead-binding protein may depend on the level and duration of exposure, and some persons may have diminished capacity for synthesizing this protein (*39*).

Another potentially important lead-binding component of RBCs that may provide rapidly diminishing binding sites at moderate blood lead concentrations is the metalloenzyme δ-aminolevulinate dehydratase (ALAD). Apparently, lead ions can replace enzyme-activating zinc ions at a small number of sites on ALAD, resulting in inactivation of ALAD and elevation of 5-aminolevulinic acid (ALA) in blood and urine (*147*). Urinary ALA increases nonlinearly, perhaps exponentially, with increases in the blood lead concentration, at least at concentrations exceeding 30–40 µg/dl and possibly much lower (*132,148*). Recent findings of Wetmur and co-workers (*147*) indicate that the blood lead concentration is higher as an average in individuals with the ALAD 1-2 or 2-2 isozyme phenotypes than in individuals with the more common ALAD 1-1 isozyme phenotype.

In the present model it is assumed that the observed nonlinear relations between lead in blood and plasma, urine, or other fluids and tissues result from a decrease in the transfer rate from diffusible plasma to RBCs as the concentration of lead in RBCs increases. The available data do not clearly reveal a threshold concentration of lead in RBCs or blood at which a reduced rate of flow into RBCs should be introduced, or even if such a threshold exists. It is as-

sumed here that such a threshold does exist because a linear model appears to reproduce the data as well as a nonlinear model at commonly encountered levels of lead, and some software packages for solving compartmental models do not allow the use of nonlinear kinetics.

Because of the uncertainty regarding the magnitude (and existence) of the nonlinear threshold and saturation levels in RBCs and the potential variation in these quantities from one exposure scenario to another, these are included as user-selected parameter values of the model, although baseline values are given. It is assumed that the deposition fraction in RBCs remains at 0.24 until the lead concentration, Y, in RBCs exceeds a nonlinear threshold level, T, expressed in μg/dl RBC. If $Y > T$, the deposition fraction, D, in RBCs is given by the equation

$$D = 0.24 \times [1.0 - (Y\text{-}T)/(S\text{-}T)]^{1.5},$$

where S is an assumed saturation concentration of lead in RBCs. This is an empirically derived expression that can be used to approximate observed relations between lead in blood and that in urine or plasma (Figs. 13 and 14, respectively). When $Y > T$, the other deposition fractions in the model are increased in proportion to their baseline values to accommodate the decrease in the deposition fraction for RBCs. That is, the deposition fractions for compartments other than RBCs are increased by the factor $(1\text{-}D)/(1\text{-}0.24) = 1.316(1\text{-}D)$. The total transfer rate from diffusible plasma to all destinations is assumed to remain at 2000/day under all conditions.

Chamberlain (*18*) suggested that nonlinear kinetics of lead is evident above a blood lead concentration of about 25 μg/dl, but other researchers have suggested that virtually linear kinetics are obeyed up to levels of 35–40 μg/dl blood. As a baseline value, the nonlinear threshold concentration T is set at 60 μg/dl RBC, which corresponds to a blood lead concentration of about 25 μg/dl.

Selection of a saturation concentration, S, is complicated by its apparent dependence on the level and duration of exposure and potential variation from one person to another. As a baseline value, S is set at 350 μg/dl RBC, based on consideration of the level of BPb at which the ratios urinary lead: BPb and plasma lead: BPb begin to increase rapidly in persons exposed for a long period to high levels of lead (Figs. 13 and 14). A much lower value for S, perhaps on the order of 140 μg/dl RBC, may be better for consideration of a high, acute intake by a person with a history of low intakes (Fig. 13).

Results of controlled studies in which the blood lead level of human volunteers

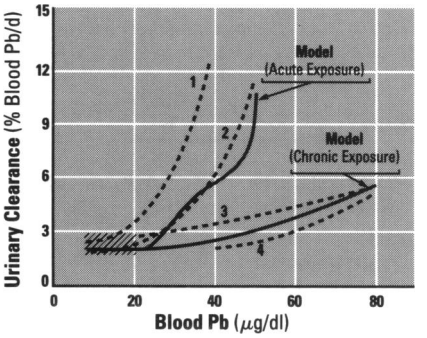


Figure 13. Model predictions (solid curves) and observations (dashed curves) of the urinary clearance of lead expressed in terms of the amount in blood. Shaded area indicates typical values for subjects chronically exposed to low levels of lead (*18,57, 115,130*). Curves 1 and 2 summarize data for two volunteers receiving a short, heavy, controlled exposure to lead (*132*). Curve 3 summarizes data of Cooper et al. (*133*) on about 300 employees of a lead smelter and refinery. Curve 4 summarizes data of Skerfving et al. (*134*) for a lead worker. Model predictions assume an exposure-dependent saturation concentration in RBCs. For an acute intake by a person with a history of low intakes, the assumed RBC saturation level is 140 μg/dl RBC. For chronic intake of high levels of lead, the assumed RBC saturation level is 350 μg/dl RBC.

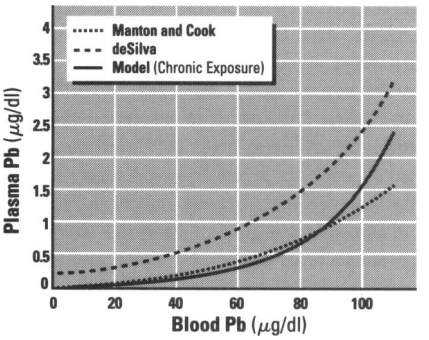


Figure 14. Model predictions and observations of the nonlinear relation between blood lead and plasma lead. The dashed curves representing observations are fits to data of Manton and Cook (*37*) or deSilva (*53*).

was increased to 35–40 μg/dl or higher over a period of weeks or months (*149–151*) seem more nearly consistent with the chronic exposure model than the acute exposure model indicated above. That is, values of S close to 350 μg/dl RBC appear to produce better agreement between model predictions and those results than do values near 140 μg/dl RBC. However, the data from those studies are too scattered and the uncertainties in the amount of lead absorbed to blood in each case are too large to draw strong conclusions in this regard. The results of Kehoe (*149*) are inconsistent with the strictly linear model described in previous sections, while the results of Griffin et al. (*150*) and Cools et al. (*151*) can be explained about as well with the linear model as the nonlinear model with S near 350 μg/dl RBC.

Modification of Parameter Values for Application to Children

ICRP Publication 56, Part 2 (*22*) introduces a generic approach for development of age-specific parameter values for calciumlike elements [also see Leggett (*91*)]. On the basis of data from a large number of studies on the fate of radioisotopes of calcium and related elements in laboratory animals and humans, it is postulated that differences with age in the biokinetics of these elements arise mainly from three related events: 1) increased fractional transfer from plasma to bone in children in association with the relatively greater rate of addition of calcium to bone in children than adults; 2) decreased fractional transfer from plasma to soft tissues and excreta in children due to relatively greater competition from immature bone; and 3) an elevated rate of transfer from nonexchangeable bone to diffusible plasma in children due to an elevated rate of bone turnover. Except where there is evidence to the contrary, removal half-times from soft tissues, bone surfaces, and exchangeable bone volume are assumed to be independent of age. For some calciumlike elements, including lead, available data are consistent with the assumption that the size of the exchangeable pool of bone is greater in children than in adults. Within the context of the present model structure or the slightly simpler structure used in ICRP Publication 56 (*22*), this means that an atom entering bone has a smaller probability of reaching nonexchangeable bone in children than in adults.

This generic approach appears to be consistent with information on the age-specific kinetics of radiolead in laboratory animals (*13,14,50,120,127,152–158*). For example, Mallon and co-workers (*13,14*) concluded from data on baboons exposed acutely or chronically to ^{210}Pb that skeletal uptake of absorbed lead was much greater in rapidly growing animals than in more mature animals. In a ^{210}Pb-ingestion experiment with 10-day-old, 150-day-old, and adult *Macaca irus* monkeys, skeletal tissues of the two younger groups contained a substantially larger portion of systemic ^{210}Pb than did those of adult monkeys at 4 days after oral dosing (*50*). In a similar experiment with rhesus monkeys, infants (ages 5–7 months) excreted a substantially smaller fraction of the absorbed amount than did adults during the first 23 days after administration (*156*).

Another perspective on differences with age in the biological behavior of lead is provided by autopsy data on human subjects exposed to environmental lead. These data can be used to derive reference organ

distributions of lead for different age groups, and these reference distributions can serve as constraints on model parameters. Several different adult populations have been studied, but reference distributions for children must be based to a large extent on data from a single study involving a large number of subjects from an industrialized region of England, including 18 subjects of age 1–10 years and 6 subjects of age 11–16 years (*114*). Thus, because of the substantial uncertainties in the accuracy and universality of the reference distributions for children, they should be treated only as first estimates rather than definitive data.

The derived reference organ distributions are indicated in Table 3, where they are represented as ranges of values rather than point estimates to emphasize the uncertainties involved. The method of development of these uncertainty ranges will be described in detail in another paper. Briefly, baseline contents (expressed as fractions of the total-body content) of lead in different tissues of a middle-aged adult male are based on medians of lead concentrations determined in the relatively detailed investigations by Gross and co-workers (*112*), Barry (*113,114*), and Tipton and co-workers (*159–161*). To reduce results from these three different studies to a common basis, reported concentrations from each study were normalized to a liver concentration of 1 ppm wet weight. Concentrations reported by Barry (*114*) were used as baseline values for the younger ages. Data from these studies were compared with findings from a variety of less comprehensive post–mortem studies in an effort to determine how well these baseline organ contents might represent an arbitrary study group. The ranges of values indicated in Table 3 were derived from a kind of parameter uncertainty analysis in which the major parameters used to derive the reference distributions were varied simultaneously within reasonable ranges of uncertainty. It was considered, for example, that 1) the relative concentrations of lead in different organs vary from one study group to another; 2) there may be problems associated with analytical techniques and contamination of samples, particularly for tissues with low concentrations of lead; 3) the sampling sites may not be representative of the whole organ or tissue; and 4) the mass of tissue represented by a reported concentration is often not well known (e.g., trabecular bone usually contains more soft tissue than bone tissue). The derived ranges of values (Table 3) cannot be interpreted as precise probability statements, but it is likely that the true relative organ contents under conditions of chronic exposure would fall within the indicated ranges.

Table 3. The distribution of lead in humans chronically exposed to a low level of lead throughout life, as calculated from postmortem data and as predicted by this model[a,b]

	Age, years[a]				
Tissue	1–5	6–9	11–16	20–30	40–50
Bone					
Postmortem data	0.45–0.80	0.50–0.80	0.55–0.85	0.75–0.90	0.85–0.95
Model prediction	0.66	0.69	0.79	0.88	0.90
Blood					
Postmortem data	0.03–0.08	0.03–0.08	0.03–0.08	0.015–0.035	0.008–0.02
Model prediction	0.045	0.055	0.04	0.025	0.02
Liver					
Postmortem data	0.05–0.10	0.05–0.10	0.04–0.10	0.03–0.07	0.015–0.035
Model prediction	0.08	0.065	0.065	0.04	0.03
Kidneys					
Postmortem data	0.007–0.015	0.006–0.015	0.005–0.010	0.003–0.007	0.002–0.004
Model prediction	0.012	0.009	0.006	0.004	0.003
Brain					
Postmortem data	0.009–0.025	0.007–0.015	0.004–0.009	0.002–0.004	0.0008–0.002
Model prediction	0.018	0.01	0.004	0.002	0.002
Other					
Postmortem data	0.12–0.35	0.10–0.32	0.08–0.30	0.04–0.15	0.02–0.08
Model prediction	0.185	0.17	0.09	0.05	0.045

[a]Values are expressed as fractions of total body lead.
[b]Model predictions are for ages 3, 7, 13, 25, and 45 years, respectively.

In the development of the present model for children, the reference distributions were first used to test provisional parameter values for children that were based on a set of generic assumptions concerning differences with age in the behavior of calciumlike elements. Some adjustments of the provisional parameter values were then made to obtain acceptable agreement between model predictions and the reference distributions for young children. It was found that the predicted age-specific distributions varied little with the exposure scenario, provided the rate of uptake of lead to blood was not radically altered over a period of a few months. Thus, predictions were based on a simple scenario of constant uptake (20 μg/day) to blood throughout life. In this model, the lead content of the various compartments at birth are derived from the assumed content in the mother's blood. The concentration of lead in blood at birth is assumed to be 0.85 times that of the mother's blood, based on a variety of studies (*162*). The relative contents of bone, blood, liver, kidneys, brain, and other soft tissues at birth are assumed to be 0.32, 0.07, 0.055, 0.01, 0.045, and 0.5, respectively, based mainly on data of Barry (*114*); for multiple-compartment organs, the contents at birth are assumed to reside in the longest-term compartment. For the exposure scenario considered here, the concentration of lead in the mother's blood is assumed to be that calculated for a 25-year-old person with chronic uptake of 20 μg Pb/day.

The provisional age-specific parameter values were based on the following generic assumptions (1–5 below), which were applied earlier to the alkaline earth elements (*22,91*).

Generic assumption 1. Fractional deposition on bone surfaces is proportional to the rate of addition of calcium due to modeling and remodeling of the given bone type (trabecular or cortical). The estimated average calcium addition rate for adults (0.25 g/day) and the deposition fraction for bone in the typical adult serve as the points of reference. The model for the rate of addition of calcium to the skeleton is described elsewhere (*91*).

Generic assumption 2. The total transfer rate from nonexchangeable bone volume is equal to the bone turnover rate and thus varies with age. The model for the rate of turnover of cortical and trabecular bone in children is described elsewhere (*21,97*).

Generic assumption 3. At all ages, cortical bone represents 80% and trabecular bone the remaining 20% of total bone (*97*). This assumption is based on measurements on the adult human skeleton (*54*). The relative amounts of cortical and trabecular bone in children cannot be estimated with much confidence, particularly for the first few years of life. As it turns out, model predictions are fairly insensitive to the division between cortical and trabecular bone in children because, as indicated by data for the alkaline earth elements and depicted in this model, there is little distinction between trabecular and cortical bone in children with regard to the kinetics of calciumlike elements. The model depicts trabecular and cortical bone as growing at the same rate and as having fairly similar remodeling rates during childhood. Bone remodeling rates are assumed to be identical in the two bone types during infancy and to diverge gradually during childhood and adolescence. As a consequence of

generic assumption 1, the estimated trabecular to cortical deposition ratio of a calciumlike element increases from 0.25 in infants (since there is assumed to be one-fourth as much trabecular as cortical bone and the growth and turnover rates are assumed to be the same for the two bone types in infants) to 0.34 at age 10 years, for example, and to 1.25 in mature adults. Bone originally laid down as trabecular bone but converted to compact bone during growth is assumed to have been cortical bone throughout its existence.

Generic assumption 4. In children, deposition fractions for soft tissues and excreta are reduced uniformly because of the higher deposition in bone. This assumption is intended to apply to the distribution that would be seen after the early, rapid exchange between diffusible plasma and extravascular fluids is largely complete. Thus, it is implemented by ignoring any potential short-term effects on the extravascular fluid compartment, EVF. Compartment EVF is assumed to receive 50% of instantaneous outflow from diffusible plasma at all ages, and reduced transfer from diffusible plasma to soft tissues and excreta of children is described in terms of the remaining 50% of outflow from diffusible plasma. As an example, the deposition fraction assigned to all bone surfaces combined is 0.08 for mature adults and, as derived from generic assumption 1, 0.24 for infants. For the infant, the deposition fractions for soft tissue compartments or excretion pathways are determined as (0.5-0.24)/(0.5-0.08) = 0.619 times the corresponding deposition fractions for adults. This approach is reasonably consistent with the limited age-specific data on lead in nonhuman primates (*13,50,156*).

Generic assumption 5. Removal half-times from soft tissues, bone surfaces, and exchangeable bone volume are independent of age. As described later, it seems appropriate to relax this assumption for the case of lead in the liver and kidneys. Also, limited information suggests that the rate of removal of alkaline earth elements from exchangeable bone may be greater in children than in adults, but the present assumption seems reasonable until age-specific rates can be better supported and quantified. Note that this assumption applies to total outflow from bone surfaces and exchangeable bone volume and does not address the destination of outflow.

A sixth assumption regarding the relative exchangeability of bone deposits in children and adults is applied in ICRP Publication 56 (*22*) on an element-by-element basis. There is evidence that exchangeability of strontium decreases with increasing bone age, but it probably should not be assumed that this phenomenon applies uniformly to all alkaline earth elements because it appears to be less pronounced for calcium than for strontium (*91*). An assumption of elevated exchangeability of bone deposits in children leads to improved agreement between model predictions and autopsy data on persons exposed to environmental ^{90}Sr and thus is applied by ICRP (*22*) to strontium. This assumption could not be tested for barium and radium and is not applied in the ICRP document to these elements. The assumption is implemented for strontium by assigning greater fractional transfer from bone surfaces to diffusible plasma in children than in adults. It could be implemented in other ways, such as by assigning a greater fractional return from exchangeable bone volume to bone surfaces in children, but the available data on strontium seem consistent with the requirement that the elevated exchange of bone strontium in children be manifested fairly rapidly.

There is no direct evidence of decreasing exchangeability of lead with increasing bone age. The situation for lead is otherwise similar to that for strontium, however, in that an assumption of elevated exchangeability of bone deposits in children helps reduce discrepancies between predictions of a provisional model based on assumptions 1–5 and autopsy data for environmentally exposed children. Therefore, the following assumption is made for lead.

Assumption 6. There is greater fractional transfer from bone surfaces to diffusible plasma in children than in adults. By analogy with strontium, it is assumed that fractional return from bone surfaces to plasma is 1.25 times higher at ages 0–15 years than in adults. For lead, this means that 1.25 × 50% = 62.5%, rounded to 65%, of the amount leaving bone surfaces goes to diffusible plasma and 35% goes to exchangeable bone volume.

As the total transfer rate from bone surfaces is assumed to be 1/day, as in adults (see generic assumption 5), the transfer rate from (trabecular or cortical) bone surfaces to diffusible plasma in children is 0.65 × (1/day) = 0.65/day, and the transfer rate from bone surfaces to exchangeable bone volume is 0.35/day.

The addition of assumption 6 improves agreement between model predictions and reference distributions for children, particularly for bone, but noticeable discrepancies remain for some compartments at some ages. For example, the liver and kidneys do not appear to be important repositories of lead in young children, but if the parameter values for adults are applied to these organs during childhood, the model predicts substantial buildup in the first few years of life, due mainly to accumulation in the long-term compartments assumed to exist in each organ. Thus, it seems reasonable to reduce the removal half-time for these compartments in young children.

Assumption 7. The removal half-time from the long-term compartments of liver and kidneys to diffusible plasma is 100 days for ages 0–5 years. The removal half-time for ages 10 years and 15 years is the same as for adults (1 year). Recall that transfer rates for ages intermediate to those indicated in Table 1 are calculated by linear interpolation (with age) of the transfer rates given in the table.

Although some discrepancies remain between model predictions and reference distributions after application of the seven assumptions indicated above, further complications of the model based on these reference distributions for children do not appear to be justified for purposes of radiation protection. For example, assumptions 1–7 yield higher fractional content in blood and lower fractional content in other soft tissues than indicated by the reference distributions for children. Estimates of dose from internally deposited radioisotopes of lead are not altered much, however, by forcing the model to fit the reference values for other soft tissues and blood; this is because the predicted and reference distributions agree reasonably well with regard to the sum of the fractional contents of other soft tissues and blood, and, in calculation of radiation doses, radiological decays in blood are assigned primarily to the organs and tissues making up other soft tissues.

While the ability to predict the level of lead in blood in chronically exposed children may not be critical for radiation protection purposes, the BPb level is the primary index used in the development of exposure guidance for stable lead. Thus, for consideration of lead as a chemical toxin, it seems worthwhile to introduce greater detail into the model to reproduce more closely the fractional contents in blood indicated by the reference distributions for children.

Data on nonhuman primates (*13,50*) suggest that there may be smaller uptake of lead by RBCs and/or faster removal from RBCs in young animals than in mature animals. Also, model predictions for children can be brought into line better with reference fractional contents of blood in children and data on intakes and blood levels of lead in infants (*163*) by assigning to the younger age groups either a smaller deposition fraction to RBCs or a shorter removal half-time to RBCs. There is little basis for choosing between these two approaches, except that within the present scheme it is simpler to assign a shorter removal half-time.

Assumption 8. The removal half-time from RBCs is shorter in young children than in adults. The following removal half-times from RBCs to diffusible plasma are chosen for reasonable consistency with the reference distributions: ages 0–1 years, 1.5 days; ages 5 years, 2.5 days; ages ≥ 10 years, 5 days.

The derived reference distributions indicate that the fractional content of other soft tissues is considerably greater in young children than in adults. The relatively high content estimated for this group of tissues at young ages can be traced to the high portion of the body weight represented by skin and fat and the high reported concentrations of lead in fat in young children compared with adults. The high reported concentration of lead in fat in children could be partly an artifact of the autopsy data, given the considerable technical problems in obtaining representative samples of fat and accurately determining the low concentrations of lead in those samples on a fresh–weight basis. In this model, the indicated higher content of other soft tissues is taken at face value and is explained by a higher deposition fraction for compartment ST1 because of its association with skin and fat. The elevated uptake by ST1 is balanced by reducing inflow to the rapid-turnover soft-tissue compartment, ST0, one of whose purposes in this model is to receive leftover lead after the other compartments have been addressed.

Assumption 9. The deposition fraction in the intermediate-turnover compartment, ST1, is two times higher at ages 0–15 years than in adults. The higher deposition in ST1 at these ages is balanced by lower deposition in ST0.

The brain is not considered as a separate organ in ICRP's model for lead (*22*) but is part of other soft tissues. Although autopsy results indicate that the concentration of lead in brain may be lower in children than in adults, the brain is estimated to contain a much higher portion of total body lead in infants and young children than adults because of its relatively greater mass (as a percentage of total body mass) at the younger ages. This is supported by comparative data on mature and immature baboons administered radiolead (*18*). In this model, the relatively higher content of brain at young ages is explained by a higher deposition fraction for brain.

Assumption 10. The deposition fraction in brain is three times higher at ages 0–1 years than in adults, due to the relatively greater mass of brain as a percentage of total body weight. The deposition fraction for brain is assumed to decline linearly with age to 5 years, when the adult value is reached. The higher deposition in brain at ages 0–5 years is balanced by assigning a slightly lower deposition fraction to ST0.

Summary and Conclusions

Several different types of information contribute to our understanding of the behavior of lead in the human body. These include results of lead tracer studies on healthy adult human volunteers; measurements of lead in autopsy samples from environmentally exposed humans of all ages; results of lead balance studies on adult humans; bioassay data and autopsy measurements on persons occupationally exposed to lead; data from controlled studies of the behavior of radiolead in laboratory animals at different stages of life; and data on the age-specific kinetics of the chemically and, in many respects, physiologically similar alkaline earth elements in humans and laboratory animals.

In this paper an attempt has been made to synthesize all of the different sources of information into an age-specific biokinetic model for lead. The data were organized within a compartmental model structure originally developed for consideration of the age-specific biokinetics of a class of calcium-like radionuclides. The model structure represents a compromise between biological realism and practical considerations regarding the quantity and quality of information available to determine parameter values. Transport of lead between compartments is assumed to follow linear, first-order kinetics provided the concentration in red blood cells remains below a nonlinear threshold level, but a nonlinear relation between plasma lead and red blood cell lead is modeled for concentrations above that level.

The model appears to be a fairly accurate predictor for adult humans exposed to relatively low levels of lead. It is proposed only as a reasonable starting point for modeling the biokinetics of lead in children or the kinetics of lead at high levels of exposure. The modular design of this model is intended to allow researchers to modify specific parameter values or model components to address special problems in lead toxicology or to incorporate new information. For example, one could substitute a detailed model of the brain for the present single-compartment brain without adjusting other components of the model.

Appendix

Respiratory and Gastrointestinal Tract Models for Lead

Respiratory Tract Model

Fractional deposition of inhaled lead in the lungs varies with the size of the inhaled material, the breathing rate, and other factors. A value of about 0.35–0.40 may be a reasonable central estimate, but deposition fractions as low as 0.15 or as high as 0.75 may not be uncommon (*18,27,31,42,44,45,128,150,164*).

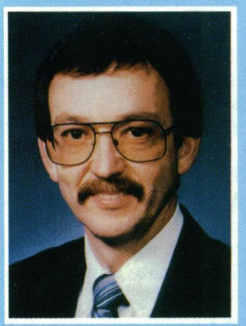
Experimental data for human subjects indicate that 85% or more of deposited lead is cleared from the lungs with an effective biological half-time on the order of 0.2–0.6 day, if clearance is expressed in terms of one or two components (*27,31,32,42,44,45,165,166*). Similarly, a biological half-time of about 0.5 day has been found for dogs (*167*). A more detailed description was given by Chamberlain and co-workers (*27*), who found that for deposited ^{203}PbO, $^{203}Pb(NO_3)_2$, or "clean" ^{203}Pb-labeled exhaust aerosols, approximately 22% was cleared with $T_{1/2}$ = 0.8 hr, 34% with $T_{1/2}$ = 2.5 hr, 33% with $T_{1/2}$ = 9 hr, and 12% with $T_{1/2}$ = 44 hr. For carbonaceous ^{203}Pb-labeled exhaust aerosols, approximately 29% was cleared with $T_{1/2}$ = 0.5 hr, 50% with $T_{1/2}$ = 4.5 hr, 6% with $T_{1/2}$ = 24 hr, and 15% with $T_{1/2}$ = 220 hr.

Fractional uptake of deposited lead to blood depends on the form and particle size of inhaled lead. For submicrometer aerosols there appears to be little ciliary clearance of deposited lead. For example, results of Hursh et al. (*42*) and Wells et al. (*32*) indicate that about 95% of deposited lead was absorbed directly to blood. When inhaled as a vapor, as much as 35–40% of deposited lead might be removed to the stomach, and the rest is absorbed directly to blood (*31*).

Based on the above information, the following lung model was adopted for comparison of model predictions with observations on the behavior of inhaled lead. The deposition fraction for unknown forms of lead is set at 0.37. (A lung deposition fraction was not needed for present purposes, because data from inhalation studies were related to the deposited amount rather than the inhaled amount.) Of the deposited amount, 20% is assumed to be cleared with $T_{1/2}$ = 1 hr, 35% with $T_{1/2}$ = 3 hr, 35% with $T_{1/2}$ = 9 hr, and 10% with $T_{1/2}$ = 2 days, with 95% of cleared lead absorbed directly to blood and 5% moving to the stomach via ciliary clearance. Greater ciliary clearance may be expected in industrial exposures, where aerosol particles are often larger (*18*), or with lead inhaled as a vapor (*31*). It is assumed that the behavior of lead deposited in the lungs is independent of age.

Gastrointestinal Tract Model

For persons ≥ 18 years old, movement of lead through the gastrointestinal tract is assumed to follow the gastrointestinal tract model of the ICRP (*12*). That is, material is assumed to move in sequence through four segments of the GI tract: stomach (S), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI). Absorption from the gastrointestinal tract is assumed to occur only in segment SI.



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Transfer from one segment to another is assumed to follow first-order kinetics. In adults, transfer rates out of segments S, SI, ULI, and LLI are 24, 6, 1.85, and 1/day, respectively. For children age 0–12 years, the removal half-time from each segment is assumed to be 0.6 times the adult value, based on data of Corazziari and co-workers (*168*). Values for ages 12–18 years are based on interpolation of the 12-year and 18-year values. Lead transferred from the liver or from plasma into the contents of the gastrointestinal tract is assigned to segment SI and is assumed to be reabsorbed to plasma at the same rate as ingested lead.

Absorption of lead from the gastrointestinal tract has been studied extensively and depends strongly on a variety of factors, including the level of calcium, phosphorus, zinc, iron, fat, protein, and vitamin D present in the intestines; the body's iron or zinc status; the amount of lead administered; the physical and chemical form administered; and the time of fasting (*6,13,169–175*). It is not surprising, then, that a large range of gastrointestinal absorption fractions (0.01–0.8) have been reported. Most measurements on adult humans have fallen in the range 0.03–0.2 for intake with solids (*9,27,173,176–180*), 0.08–0.30 for intake with liquid between meals (*27,181*), and 0.3–0.7 for ingestion with liquids after several hours of fasting (*9,27,173,177,179,180*). Most balance studies have indicated values of 10% or less (*101,149,182–184*), but reanalysis of balance data in view of current information on endogenous fecal excretion of lead indicates that an estimate of 0.15 or greater might be more appropriate (*27,128*).

Balance studies suggest that infants and children may absorb 40% or more of ingested lead (185–188), but results of these studies are highly variable and inconclusive. Data on monkeys (*50,156*) and rats (*152,157,189,190*) generally indicate substantially higher absorption of lead in growing than in mature animals.

In ICRP Publication 56 (*22*), absorption fractions assigned to infants, ages 1–15 years, and adults are 0.6, 0.4, and 0.2, respectively. In this paper the same pattern is assumed, but the values are reduced by 25%, to 0.45 in infants (defined here as 0–100 days of age), 0.3 at ages 1–15 years, and 0.15 in adults (≥ 25 years). Linearly interpolated values are used for ages between 100 days and 1 year or between 15 years and 25 years. For example, the value for age 20 years is $(0.5 \times 0.3)+(0.5 \times 0.15) = 0.225$.

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